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17 Nonclassic Cystic Fibrosis in subjects with D1152H CFTR mutation

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Rationale: Limited knowledge exists on phenotypes associated with the D1152H cystic fibrosis transmembrane conductance regulator (CFTR) mutation.
Objectives: To characterize phenotypes in subjects with a D1152H allele in trans with another CFTR mutation.
Methods: D1152H subjects were identified using the French Cystic Fibrosis (CF) Registry. Phenotypic characteristics were compared with those of CF subjects in the Registry (Controls).
Main Results: Forty two subjects with D1152H alleles were identified. Diagnostic features included chronic sinopulmonary disease (n = 25), congenital absence of the vas deferens (n = 11), systematic neonatal screening (n = 4), and genetic counseling (n = 2). Excluding systematic neonatal diagnosis, median age at diagnosis was 33 (interquartile range, [24–41]) yr in D1152H subjects and was 0.58 [0.17–3.67] yr in Controls ($P < 0.001$). Median sweat chloride concentrations were 43.5 [39–63] mmol/l in D1152H subjects vs. 100 [83–118] mmol/l in Controls ($P < 0.001$). Only 10/42 (24%) D1152H subjects had classic CF. Nonclassic CF (sweat chloride $\leqslant$60 mmol/l and compatible clinical manifestations) was present in 26/42 (61.9%) D1152H subjects; 6/42 (14.3%) D1152H subjects were asymptomatic. Bronchiectasis was present in 67% of D1152H subjects, but *Pseudomonas aeruginosa* colonization and pancreatic insufficiency were present in <30% of subjects. Estimated rates of decline in FEV1 and in FVC were lower in D1152H subjects vs. Controls ($P < 0.001$). None the D1152H subjects identified since 1999 died or had lung transplantation despite an elevated age at last evaluation.
Conclusions: D1152H is a mutation that when present in trans with a CF-causing mutation causes variable phenotypes, often characterized by nonclassic (mild) cystic fibrosis.
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18 Cystic Fibrosis and mitochondrial gene mutation MT-RNRI

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Patients with CF are, due to the colonization of *Pseudomonas aeruginosa*, *Burkholderia cepacia* and other pseudomonal bacteria, very often treated with aminoglycocides (AG) in combination with beta-lactams, maybe the one cohort treated most often and heavily with AG. Some patients do acquire a loss of hearing, which has been seen as an unfortunate side effect of too much or too high of a dose of AG. At the same time 15–25%, maybe as much as 70% of patients with hearing problems have been found to have a mitochondrial gene mutation (MT-RNRI), which can already when a first dose of AG is given, cause severe hearing problems. It seems important to find this mutation early in the CF group, not to cause hearing disability unnecessarily. We are therefore screening all our patients for this mutation and will report on the result.

19 Occurrence of complex CFTR alleles, revealed by extensive mutational analysis, can account for high sweat test variability

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In a cohort of 416 CF patients from Central Italy affected by typical CF forms, a two-step preliminary investigation of the most common CFTR mutations (32 worldwide + 20 regional-specific) was completed – when it had failed to identify two disease-causing mutations – by an extensive sequencing of all exons and of the adjacent intronic zones and by a search of the 6 most frequent deletions. The allelic detection rates raised, throughout these four steps, from 77.2% to 85.9%, then to 97.2% and finally (when also deletions were investigated) to 98.5%. The genotypic detection rates (with the identification of at least 1 mutation per allele) grew correspondingly from 60.6% to 74.1%, then to 95.3% and finally to 97.4%. No identification of disease-causing mutations occurred only in 12 CFTR alleles (10 in subjects with a known mutation on the other allele and 2 in the alleles of a single patient). The mutational patterns of the other 405 CF patients could be grouped into 15 different "homogeneously mutated" genotypes.
A wide variability in the sweat test values occurred however even among subjects having the same apparently homogeneous genotype. By performing the extensive mutational analysis even on alleles where a mutation had already been identified, we could often account for this sweat test variability by showing the occurrence of a complex allele that was affected by more than a single disease-causing mutation.
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20 Analysis of eNOS, TNFA, LTA, GSTM1, MBL2, ADRB2, HFE genes as modifier genes in Russian Cystic Fibrosis patients

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Recent investigations have been established that polymorphic variants in genes besides CFTR play an important role in determining severity of CF disease. We analyzed the association of CF clinical features and polymorphisms/mutations in 6 genes: VNTR polymorphism in intron 4 of eNOS gene; –308 G-A of TNFA gene; +252 A-G of LTA gene; 10 kbp deletion polymorphism of GSTM1 gene; promoter polymorphism –221G-C and 3 mutations in exon 1, G54D, G57E, R52C, of MBL2 gene; R16G, Q27E of ADRB2 gene; C242Y and H63D of HFE gene in 148 CF patients homozygous for F508del mutation. Patients were categorized into groups according to their genotypes of analyzing genes. The age of lung and intestinal disease manifestation, the age of diagnosis, severity of disease progression, FVC and FEV1 indexes, height-weight indexes, *S. aureus* and *P. aeruginosa* colonization, liver disease and meconium ileus (MI) were evaluated. We revealed the association of eNOS, MBL2 and HFE genes and disease severity. Patients carrying A allele of the eNOS gene (genotypes A/A and A/B) had significantly lower pulmonary function ($p < 0.05$); airways colonization by Ps. aeruginosa were diagnosed significantly earlier in patients with MBL-insufficient alleles ($p < 0.02$); liver cirrhosis was more frequent among patients with B/B genotype of the eNOS gene ($p < 0.05$); and meconium ileus was more frequent in patients carrying D63 allele of HFE gene($p < 0.05$). Associations between phenotypic characteristic of CF and analyzed polymorphisms of TNFA, LTA, ADRB2 and GSTM1 genes were not found.
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